Off-Pump Coronary Artery Bypass Grafting: 30 Years of Debate

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Off-pump coronary artery bypass surgery (OPCAB) has been performed for >30 years.

The promotion of OPCAB was based on its potential benefits over some of the limitations of traditional on-pump coronary artery bypass surgery (ONCAB) by avoiding the trauma of cardiopulmonary bypass (CPB) and by minimizing aortic manipulation. As such, reductions in early mortality and perioperative neurological events, renal failure, blood product transfusions, and hospital length of stay were expected according to the OPCAB proponents. In contrast, critics of OPCAB remain concerned about incomplete and/or poorer quality coronary revascularization with a potential increase in the need for repeat revascularization and late mortality.

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Despite 3 decades of debate, 115 randomized trials, and >60 meta-analyses comparing on- and off-pump coronary artery bypass grafting (CABG), controversy on both the role of and indications for OPCAB remains vigorous.

In this review, we provide a comprehensive update of the evidence for the differences in the biological effects of off- and on-pump surgery and the comparison of the clinical and angiographic results of the 2 techniques. Furthermore, we critically address the relevant technical aspects of OPCAB, the importance of surgeon experience, and the difference in the costs for the 2 procedures.

Search Strategy

The Arterial Grafting International Consortium (ATLANTIC) Alliance is an international writing group on coronary surgery. In January 2018, a comprehensive search to identify studies that evaluated the biological, clinical, angiographic, and economic aspects of OPCAB was performed in the following databases from inception to present: Ovid Medline, Ovid Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register). Search keywords included *myocardial revascularization* in combination with *coronary artery bypass, on pump, off pump*, and *OPCAB.* Relevant abstracts were reviewed, and the related articles function was used for all included studies. References for all selected studies were cross-checked. The writing group selected the most relevant papers according to both methodological and clinical considerations. Observational series were considered only in the absence of data from randomized controlled trials (RCTs).

The Technical Evolution of Beating-Heart Coronary Artery Bypass Surgery

The very first direct coronary revascularization procedures in the early 1960s were performed on the beating heart without CPB.[1] However, the technique was soon abandoned because of developments in extracorporeal circulation and improvement in myocardial protection that made the surgery safer, standardized, and reproducible. In the early 1980s, 2 South American surgeons, Buffolo[2] and Benetti,[3] published their extensive series of OPCAB. Most patients received grafts to the left anterior descending coronary artery (LAD) and the main right coronary artery, but with more limited and difficult grafting of coronary arteries on the posterior and lateral wall. In the mid 1990s, a minimally invasive left internal mammary artery (LIMA)–LAD performed through a small left anterior thoracotomy on the beating heart[4] was proposed in combination with percutaneous coronary intervention (PCI) for the non-LAD targets.[5]

Innovative technology played a key role in the development of OPCAB by minimizing the motion of the heart during construction of the anastomosis. Initially, stabilization of the target coronary vessel was obtained by stay sutures, but the advent of mechanical stabilizers, by means of pressure or suction pods, transformed the way OPCAB was performed, accompanied by an evident improvement in surgical results.[6] The critical challenge was the exposure of the lateral and inferior walls. Initially, lifting of the heart and exposure of the targets were achieved with multiple slings[7] or pericardial stitches, as proposed by Lima and Salerno.[8] The commercialization of pressure- and vacuum-assisted positioners further changed the field and allowed minimization of hemodynamic changes during exposure. The use of intracoronary shunts rather than snaring of the target native coronary vessel has been shown to significantly reduce intraoperative myocardial dysfunction and hemodynamic instability during OPCAB.[9]

The use of a transit-time flowmeter, high-resolution epicardial ultrasound, or intraoperative fluorescence imaging allowed intraoperative control of the quality of the anastomosis, an issue of particular relevance during the technically more complex OPCAB procedure.[10]

For the future of OPCAB, technology will play an increasingly important role with the adoption of hybrid revascularization and robotic assisted OPCAB. The concept of hybrid coronary revascularization (HCR) stems from the hypothesis that the LIMA-LAD graft is superior to coronary stenting of the LAD, whereas contemporary drug-eluting stent–PCI is noninferior to venous bypass grafts used for non-LAD targets. Although still limited to sporadic experiences in dedicated centers, HCR has the potential to combine the advantages of minimally invasive OPCAB with complete coronary revascularization.

The use of robotic assistance during CABG has been associated with superior cosmetic results and reduced postoperative pain but also longer operative times and higher costs.[11]

Differences in Systemic Inflammatory Reaction and Platelet/Coagulation Activation After On- and Off-Pump CABG

CABG elicits a complex prothrombotic and proinflammatory response that peaks within a time frame spanning from the end of CPB to the early hours thereafter. These molecular changes may persist for days or weeks after CABG.[12] In particular, several studies have described marked and protracted activation of several molecular pathways, reflecting a systemic inflammatory reaction, platelet and coagulation activation, and increased oxidative stress and endothelial dysfunction.[13] Interestingly, these changes appear to occur after both ONCAB and OPCAB, with a relatively limited number of these pathways (eg, oxidant stress) showing more pronounced activation in the presence of CPB.[13]

Systemic Inflammatory Reaction

Patients undergoing CABG constitute a distinct high-risk group characterized by advanced atherosclerotic disease, low-grade systemic inflammation, and the clustering of several other comorbidities.[13] The CABG operation per se is a potent triggering factor for cardiovascular events because it elicits major endocrine stress and systemic inflammatory response, which involves the release of acute-phase proteins and sepsis-like symptoms during postoperative recovery.[14,15] The inflammatory response during CABG may be related, at least in part, to the use of CPB that induces leukocyte and platelet activation, thrombin and plasmin-mediated procoagulant and fibrinolytic effects, and a rapid and sustained multifold increase in the circulating levels of proinflammatory mediators.[16] Myocardial tissue ischemia as a result of aortic cross-clamp, reperfusion injury, plaque rupture and microembolization, and other factors (eg, type of anesthesia) also may play a role in CABG-related inflammation.[17]

If and to what extent avoidance of CPB can reduce or even eliminate the systemic inflammatory reaction after surgery is controversial. Studies that evaluated the circulating levels of proinflammatory cytokines (IL-6, -8, and -10) after off- and on-pump- surgery reported contradictory results.[14,18–22]

The concomitant use of cardiotomy suction or non–heparin-bounded CPB circuits in some of the trials is a plausible cause of heterogeneity and may partially explain the contradictory results.

Interestingly, the severity of the inflammatory response to OPCAB might be affected by the type of anesthesia.[23] Inflammation has been proposed to have an important role in determining early postoperative complications (eg, low-output syndrome, myocardial injury, and atrial fibrillation or stroke). Indeed, increased preoperative CRP (C-reactive protein) levels are independently associated with early and late mortality in CABG patients.[24] In other studies, preoperative levels of IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein 1) predict postoperative atrial fibrillation development in CABG patients.[25] Gaudino et al[26] described a significant correlation between a single-base promoter mutation of the polymorphism of the *IL6* gene, the postoperative level of IL-6, and the development of pulmonary and renal complications and atrial fibrillation after CABG. In RCTs, OPCAB has been associated with significantly lower myocardial injury and increase in inflammatory mediators compared with ONCAB,[14,15] although early mortality rates did not differ significantly.[27] Nevertheless, it must be noted that the results of pharmacological treatment aimed at reducing the postoperative inflammatory reaction after CABG (corticosteroids, statins) have been mixed,[28,29] so the role of attempts to modulate inflammation in determining postoperative clinical outcome after CABG remains to be determined.

Platelet and Coagulation Activation

Activation of the plasmatic and cellular components of the hemostatic system occurs through 2 distinct mechanisms, namely, contact of blood with the surgical wound and contact of blood with the foreign surface of the CPB circuit.[30] The former plays a major role in the early activation of the hemostatic system that results in thrombin generation. Besides catalyzing the conversion of fibrinogen to fibrin, thrombin has multiple cellular targets (both in blood [eg, platelets] and the vessel wall) through the interaction with protease-activated receptors.[30,31] Moreover, there is bidirectional interplay between blood coagulation and inflammation, with activation of the former leading to an inflammatory reaction and vice versa.[30] Circulating platelets are activated during CABG by several distinct mechanisms, including thrombin interacting with platelet PAR-1 (protease-activated receptor 1), interaction with fibrinogen bound to the CPB circuit, and contact with foreign surfaces. These activation processes eventually lead to reduced numbers of circulating platelets and perioperative platelet dysfunction.[30] Moreover, activated platelets release a broad range of inflammatory mediators, thereby reinforcing the inflammatory reaction.[31] The increased vascular biosynthesis of the antithrombotic prostanoid prostacyclin (PGI_2) represents a homeostatic response to inflammation and platelet activation.[32]

A limited number of studies have compared the effects of ONCAB versus OPCAB on platelet activation and aggregation and failed to demonstrate major differences between them.[30,33–35] It should be emphasized that these studies relied on measurements of platelet function ex vivo, which do not necessarily reflect the extent of platelet activation in vivo.[31]

A different and more clinically relevant way of assessing the potential hemostatic/prothrombotic differences related to ONCAB versus OPCAB is represented by studies of the pharmacodynamic response to antiplatelet drugs in these settings.[32,33] In a study by Zimmermann et al,[33] the antiplatelet effect of aspirin (100 mg/day started on day 1 after surgery) evaluated at day 5 was largely impaired after CPB but not after CABG without CPB; therefore, increased platelet turnover after CPB appears to contribute to transient aspirin "resistance" because an increased number of new platelets might be competent to form Thromboxane A_2 (TXA_2) within the 24-hour dosing interval.[33] Consistent with this hypothesis, Cavalca et al recently reported impaired aspirin pharmacodynamics early after ONCAB that were associated with significant increases in immature platelets, total platelets, platelet mass, thrombopoieitin, IL-6, glycocalicin, leukocytes, and high-sensitivity CRP.[32] IL-6 can control inflammation through CRP and modulate megakaryocyte fragmentation, differentiation, and platelet release directly or through thrombopoieitin.[32] Changes in thrombopoietic indexes were largely reversible 3 months after surgery.[32] As shown by 3 independent studies, shortening the dosing interval (ie, twice-daily dosing), but not doubling the dose, safely rescued the impaired antiplatelet effect of low-dose aspirin and prevented platelet activation associated with acute inflammation and enhanced platelet turnover following cardiac surgery.[32,36,37]

To summarize, at present there is no clear-cut demonstration of a substantial reduction of the postoperative systemic inflammatory reaction and platelet activation after OPCAB. The antiplatelet effect of low-dose aspirin is transiently impaired following ONCAB because of enhanced platelet turnover.

Comparison of Short-Term Clinical Outcomes of On- and Off-Pump CABG

The benefits and risks of OPCAB have been the subject of several large RCTs, observational studies and registries, and >60 meta-analyses. In the largest randomized comparisons (CORONARY [CABG Off or On Pump Revascularization] and ROOBY [Randomized On/Off Bypass] trials), there were no differences in the primary study end point at 30 days.[27,38] In CORONARY,[27] the primary composite outcome of death, nonfatal stroke, or nonfatal myocardial infarction (MI) was similar between OPCAB and ONCAB (9.8% versus 10.3%, P=0.59). Similarly in ROOBY, the primary composite outcome of 30-day death or major complications was similar between the 2 arms (7.0% versus 5.6%, P=0.19).[38] Furthermore, there was no difference in any individual component of these early composite outcomes (Table 1). Consistent with the purported benefits of off-pump surgery, several other perioperative complications (transfusion, reoperation for bleeding, acute kidney injury, and respiratory complications) were reduced in the off-pump patients in CORONARY.

Table 1. Early and Late Outcomes of ONCAB Versus OPCAB

Trial	Median Follow-up	Interventions	Early Outcomes				Late Outcomes					MACCE Definition
			Mortality	RR	Stroke	MI	Mortality	Stroke	MI	RR	MACCE	
CORONARY[39]	4.8 y	ONCAB	59/2377 (2.5)	4/2328 (0.2)	27/2377 (1.1)	170/2377 (7.2)	322/2377 (13.5)	66/2377 (2.8)	194/2377 (8.2)	55/2377 (2.3)	560/2377 (23.6)	Death from any cause, nonfatal MI, nonfatal stroke, new renal failure requiring dialysis, RR
		OPCAB	60/2375 (2.5)	16/2330 (0.7)	24/2375 (1.0)	158/2375 (6.7)	346/2375 (14.6)	55/2375 (2.3)	178/2375 (7.5)	66/2375 (2.8)	548/2375 (23.1)	
ROOBY[40]	5 y	ONCAB	13/1099 (1.2)	8/1099 (0.7)	8/1099 (0.7)	17/1099 (1.8)	131/1099 (11.9)	···	105/1099 (9.6)	131/1099 (11.9)	131/1099 (11.9)	Death from any cause, acute MI, RR
		OPCAB	18/1104 (1.6)	8/1104 (0.7)	14/1104 (1.3)	15/1104 (1.7)	168/1104 (15.2)	···	134/1104 (12.1)	145/1104 (13.1)	145/1104 (13.1)	
GOPCABE[41]	1 y	ONCAB	34/1207 (2.8)	5/1207 (0.4)	32/1207 (2.7)	20/1207 (1.7)	95/1191 (8)	52/1191 (4.4)	28/1191 (2.4)	24/1191 (2.0)	167/1191 (14)	Death from any cause, MI, stroke, RR, new renal failure requiring dialysis
		OPCAB	31/1187 (2.6)	15/1187 (1.3)	26/1187 (2.2)	18/1187 (1.5)	83/1179 (7)	41/1179 (3.5)	25/1179 (2.1)	36/1179 (3.1)	154/1179 (13.1)	

Data are shown as frequency (percentage). CABG indicates coronary artery bypass grafting; CORONARY, CABG Off- or On-Pump Revascularization; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; MACCE, major adverse cardiovascular or cerebral events; MI, myocardial infarction; ONCAB, on-pump coronary artery bypass surgery; OPCAB, off-pump coronary artery bypass surgery; ROOBY, Randomized On/Off Bypass; RR, repeated revascularization.

In GOPCABE (German Off-Pump CABG in Elderly Trial), a German RCT including only patients aged >75 years, there was no significant difference in the primary composite end point of death, stroke, MI, or new renal replacement therapy (7.8% versus 8.2%, P=0.74) at 30 days[41] and no differences in the individual components of the composite end point (Table 1). However, there was an increased number of repeat revascularizations with OPCAB (1.3% versus 0.4%, P=0.04), a finding also observed in CORONARY (0.7% versus 0.2%, P=0.01).

Of note, no reduction in stroke was noted both in hospital and at 1 year (CORONARY: 1.5% versus 1.7%; [hazard ratio (HR): 0.90; 95% confidence interval (CI), 0.57–1.41]; GOPCABE: 3.5% versus 4.4%; P=0.26).[41,42]

At 12 months, the primary composite end point was not different in the OPCAB and ONCAB patients in GOPCABE (13.1% versus 14.0%; P=0.48) or in CORONARY (12.1% versus 13.3%; P=0.24). In ROOBY, the primary outcome favored on-pump surgery (9.9% versus 7.4%; P=0.04), as did death from cardiac causes (2.7% versus 1.3%; P=0.03).

In contrast to the randomized trials, large propensity-matched databases have reported superior short-term outcomes with OPCAB, particularly in higher risk patients.

Polomsky and associates, using data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) on 876 081 elective isolated CABG operations, found that the odds ratios (ORs) for death and most major complications were significantly lower with OPCAB than with ONCAB.[43]

A meta-analysis of 35 propensity-matched studies and 123 137 patients found OPCAB to be superior to on-pump surgery for all short-term outcomes including mortality.[44]

To summarize, RCTs have reported similar operative risk for off- and on-pump CABG, whereas single-center studies have reported better outcomes, particularly in high-risk patients.

Comparison of Long-Term Clinical Outcomes of On- and Off-Pump CABG

Conflicting evidence exists on whether off-pump CABG is associated with inferior long-term outcomes. At 5 years, there was no difference in the primary outcome in the CORONARY trial.[39] In the ROOBY trial, however, 5-year survival was significantly worse in the off-pump group (15.2% versus 11.9%; P=0.02).[40] Event-free survival was also significantly decreased in the off-pump group (31.0% versus 27.1%; P=0.05), along with MI and the need for repeat revascularization (Table 1).

In a single-center observational study of 12 812 patients from Emory University, Atlanta, GA, USA, there was no difference in 10-year mortality between on- and off-pump surgery after propensity score covariate adjustment (HR: 1.00; 95% CI, 0.88–1.14).[45] Importantly, the authors reported that the key to long-term survival was completeness of revascularization in both on- and off-pump patients. Similarly, in 942 propensity score–matched patient pairs from a single Italian center, there was no difference in 10-year mortality between on- and off-pump surgery (HR: 1.3; 95% CI, 0.91–1.9).[46] In a study from the United Kingdom of >13 000 propensity-matched patients followed for 13 years, there was no difference in survival, suggesting that when OPCAB is performed by highly experienced surgeons, there is no adverse effect on survival.[47]

In contrast, a propensity-matched single-institution study from Baylor Research Institute, Dallas, TX, USA showed an elevated risk of late mortality at 10 years with OPCAB (HR: 1.18; 95% CI, 1.02–1.38).[48] These concerns about late mortality were further explored in a meta-analysis of 42 RCTs and 31 risk-adjusted observational studies that included 1.2 million patients.[49] OPCAB was associated with a statistically significant 10% relative increase in the probability of mortality at 5 years (95% CI, 5.0–15.0%) that increased to 14% at 10 years in the observational studies (95% CI, 11.0–17.0%). It is important to note, however, that although statistical significance was reached, the clinical relevance of the reported difference remains to be determined (absolute difference: 0.5% at 5 years and 3% at 10 years).

The most recent meta-analysis including only RCTs with ≥4-year outcome and pooling data from 8145 participants reported an OR for long-term mortality of 1.16 for OPCAB (95% CI, 1.02–1.32).[50]

To conclude, long-term data are discordant. Based on the current evidence, the possibility that off-pump surgery results in worse clinical outcomes cannot be excluded.

OPCAB in Specific Subsets of Patients

High-Risk Populations

Multiple studies have suggested a benefit of OPCAB in high-risk patient populations. A recent meta-analysis of RCTs demonstrated a significant relationship between the patient risk profile and the benefits from OPCAB, with the most benefit derived from reduced perioperative morbidity.[51]

An analysis of the STS ACSD from 1997 to 2007 showed that there were 38% and 55% reductions in the odds of early mortality for patients undergoing off-pump operations in the third- and fourth-highest risk quartiles, respectively.[52] In contrast, a study of the Australian and New Zealand Society of Cardiac and Thoracic Surgeons database for high-risk patients associated OPCAB with reduced morbidity but showed similar operative mortality as compared to ONCAB.[53]

Impaired Ventricular Function

As for patients with low ejection fraction (EF), an analysis of the STS ACSD from 2008 to 2011 of 25 667 patients with low

EF (<30%) found that the risks of death, stroke, and major adverse cardiac events (MACE) were lower in the OPCAB group.[54] These findings were corroborated by analysis of the Japan Adult Cardiovascular Surgery Database in which OPCAB was associated with reduced early morbidity and mortality in patients with EF <30%.[55] A meta-analysis of observational studies concluded that OPCAB may be associated with lower incidence of early mortality in patients with impaired left ventricular function but noted that the method of handling the conversion-related mortality in each study was uncertain and may have influenced the results. In addition, incomplete revascularization (IR) in the OPCAB group occurred more often and may explain why the early advantage in mortality was not maintained long term.[56]

Advanced Age

Advanced age is a known risk factor in CABG.[57] In a systematic review of 16 observational studies of CABG in octogenarians (18 685 ONCAB and 8938 OPCAB), in-hospital mortality (pooled OR: 0.64; 95% CI, 0.44–0.93; P=0.02), and stroke (pooled OR: 0.61; 95% CI, 0.48–0.76; P<0.001) were significantly lower in OPCAB.[58] However, results from a Danish registry did not show a difference in outcomes between ONCAB and OPCAB in patients aged >70 years.[59] A propensity matched study of 6943 pairs of octogenarians showed a 30% reduction in the odds of stroke with OPCAB using the Nationwide Inpatient Sample (NIS).[60] In addition, the largest RCT to date comparing OPCAB and ONCAB in elderly patients (aged ≥75 years), reported no significant difference between ONCAB and OPCAB with regard to the composite outcome of death, stroke, MI, repeat revascularization, or new renal replacement therapy within 30 days and 1 year after surgery.[41]

Female Sex

Numerous studies report CABG mortality to be higher in women.[61,62] In fact, according to the STS CABG risk model, female sex is associated with increased risk of operative mortality (OR: 1.31), major complications (OR: 1.18), and increased hospital length of stay (OR: 1.24).[57] OPCAB, however, may narrow or eliminate this disparity in outcomes between women and men. A large study at an experienced OPCAB US academic center concluded that OPCAB disproportionately benefits women and narrows the sex disparity in outcomes after CABG. Female patients (n=3248) and those treated with OPCAB (n=4492) were older and had more comorbidities than male patients (n=8165) and those treated with ONCAB (n=6921), respectively. Women treated with ONCAB had risk-adjusted ORs of 1.60 for death (P=0.01) and 1.71 for MACE (P<0.001) compared with men who had ONCAB. In contrast, women treated with OPCAB had outcomes similar to men who had either OPCAB or ONCAB. Among women, OPCAB was associated with a significant reduction in death (OR: 0.39; P=0.001) and MACE (OR: 0.43; P<0.001).[63]

These findings were replicated at a national level in an STS ACSD study of 63 experienced centers that performed >100 OPCAB cases between 2004 and 2005. Women (n=11 785) and those treated with OPCAB (n=16 245) were older and had more comorbidities than men (n=30 662) and those treated with conventional ONCAB (n=26 202), respectively. The risk-adjusted ORs for death and major complications were significantly lower with OPCAB than with ONCAB. Among ONCAB cases only, women had a significantly greater adjusted risk of death, prolonged ventilation, and longer hospital length of stay than men; however, among OPCAB cases, women had similar outcomes.[64] A meta-analysis of observational studies associated OPCAB with reduced perioperative MI but not with reduction of other morbidities or operative mortality.[65] Of note, women undergoing OPCAB received fewer grafts than those undergoing ONCAB.

OPCAB may have a selective benefit for women. The underlying mechanism is unclear and is unlikely to be related to avoidance of CPB because there is no major sex difference in outcomes associated with valve surgery.[66] It is interesting, however, that women who undergo OPCAB are more likely to receive an internal mammary artery bypass than those undergoing ONCAB.[67]

Neurological Risk

The possible association of OPCAB with reduced stroke with enhanced benefit in higher risk patients[67] argues for a potential benefit in patients with a history of atheromatous aorta or cerebrovascular disease. A large single-center study utilizing propensity-matched analysis in patients with atheromatous disease of the ascending aorta associated ONCAB with an increased risk of postoperative stroke (OR: 1.4; P=0.05) and operative mortality.[68] Another study associated OPCAB with reduced stroke and operative mortality in a similar population.[69] Patients with carotid stenosis may have a potential benefit with OPCAB,[70] but the evidence is inconclusive, and when it comes to combined CABG and carotid endarterectomy, again, the data are sparse, but both OPCAB and ONCAB may provide equivalent outcomes.[71] In patients with a history of preoperative cerebrovascular events, OPCAB does not appear to confer a risk benefit with regard to postoperative neurological outcome compared with ONCAB.[72] Of note, postoperative cognitive impairment is similar after on- and off-pump CABG.[73]

End Organ Failure

The data on the benefit of OPCAB in patients with end-organ failure, including renal failure and cirrhosis, are limited to observational studies and mostly small patient numbers. Despite a higher rate of IR, a propensity-matched analysis associated on-pump with increased operative mortality in patients with advanced chronic kidney disease.[74] A meta-analysis including 17 studies with 201 889 patients with chronic kidney disease associated OPCAB with lower early mortality (OR: 0.88; 95% CI, 0.82–0.93; $P<0.0001$) and morbidity compared with ONCAB. However, there was no difference regarding long-term survival (HR: 1.08; 95% CI, 0.86–1.36; $P=0.51$).[75] A large study based on the National Health Research Institute of Taiwan reported similar outcomes of OPCAB and ONCAB in patients on dialysis.[76] Similar findings were reported by a meta-analysis of 10 retrospective studies.[77]

Cirrhosis substantially increases the operative risk in patients who undergo cardiac surgery. In a national sample of 3 046 709 patients who underwent CABG procedures, of which 744 636 (24.4%) were OPCAB, 6448 patients (0.3%) had cirrhosis. In the overall CABG group, cirrhosis was independently associated with increased mortality (adjusted OR: 6.9; 95% CI, 2.8–17) and morbidity (adjusted OR: 1.6; 95% CI, 1.3–2.0), The OPCAB subgroup analysis revealed that the presence of cirrhosis did not affect mortality or morbidity unless there was severe liver dysfunction. In the ONCAB patients, however, cirrhosis was associated with increased mortality and morbidity regardless of the severity of liver dysfunction.[78]

In summary, the available evidence suggests that OPCAB can be associated with better outcomes in high-risk patents. Elderly patients, patients with low EF, those with high neurological risk, women, and patients with end-organ failure may benefit from off-pump surgery, although the extent of this benefit remains unclear at present.

OPCAB and Graft Patency

The effect of OPCAB on graft patency rate is still controversial. In the angiographic analysis of the ROOBY trial, the 1-year patency rate in the off-pump arm was significantly lower than in the on-pump arm. Follow-up angiography was obtained in 62% of the patients of the initial cohort. Overall patency rate was 82.6% in the off-pump group and 87.8% in the on-pump group ($P<0.001$). At least 1 occluded graft was found in 36.5% of off-pump versus 28.7% of on-pump patients (relative risk: 1.27; 95% CI, 1.09–1.48). Arterial conduits (mainly LIMA to LAD grafts) showed similar patency rates in the 2 groups (92.9% versus 94.8%; $P=0.13$), whereas saphenous vein grafts had a significantly lower patency rate in the off-pump group (76.6% versus 83.8%; $P<0.001$). Interestingly, however, both arterial and venous conduits had significantly lower perfect patency in the OPCAB group. Grafts to the posterior descending artery had the worse patency when performed off-pump (74.1% versus 82.8%; $P=0.003$).[79]

A smaller single-institution and single-surgeon RCT reported similar angiographic outcomes with the 2 techniques.[80] A Japanese RCT including 167 consecutive patients found no difference in patency but a numerically higher perfect patency rate in the on-pump group (96% versus 93%; $P=0.09$), particularly for grafts to the right coronary system (99% versus 90%; $P=0.02$).[81] A post hoc analysis of the large angiographic database of the PREVENT (The Project of Ex-vivo Vein Graft Engineering via Transfection) IV study (1920 patients and 4736 grafts) found no difference in the patency rates of the 2 techniques.[82]

All the meta-analyses report a higher incidence of graft occlusion or failure in the OPCAB arm. A meta-analysis of 12 RCTs pooling together angiographic data from 3894 (OPCAB) and 4137 (ONCAB) grafts reported an increased risk of occlusion of all grafts in the OPCAB group (relative risk: 1.35; 95% CI, 1.16–1.57), mainly due to saphenous vein graft failure (relative risk: 1.41; 95% CI, 1.24–1.60).[83] Interestingly, there was no significant difference in graft occlusion between the 2 techniques for internal mammary artery and radial artery grafts.

The most recent meta-analysis pooled angiographic data on 7011 grafts and found an OR of 1.51 for occlusion in the OPCAB arm (95% CI, 1.21–1.88; $P=0.002$).[84] Differences in surgeons' experience, varying completeness of follow-up, and angiographic definitions are the plausible reasons for the reported discrepancies. In particular, the use of overall patency in some series and perfect patency (ie patency without any irregularity) in others makes the comparison of the different studies difficult.

To summarize, OPCAB seems associated with lower patency and perfect patency rate, although contradictory results have been reported.

Completeness of Revascularization

Completeness of myocardial revascularization is a cornerstone of CABG. In a meta-analysis including aggregated data from 30 389 patients, complete myocardial revascularization had a strong protective effect against long-term mortality (HR: 0.63; 95% CI, 0.53–0.75).[85]

In most published comparative series, the number of grafts per patient in the OPCAB arm is lower than in the pump-assisted group.[86] A relation with surgeon experience seems to exist, and this has led to concerns that off-pump surgery is achieved at the expense of the completeness of the revascularization, especially when performed by less experienced surgeons.

In fact, despite technological advances, grafting the inferior and posterolateral wall off-pump can be challenging. In the ROOBY trial, the numbers of planned grafts per patient were similar in both groups (3.0 versus 3.0; P=0.98), but the number of grafts performed was inferior in the OPCAB arm (2.9 versus 3.0; P<0.001).[40] In the on-pump group, 11.1% of patients received fewer grafts than planned compared with 17.8% in the OPCAB series (P<0.001); at 5 years, the respective rates of repeat CABG were 0.5% and 1.4% (P=0.02). In the CORONARY trial,[87] however, which involved more expert off-pump surgeons, the rate of IR was similar in the 2 groups (11.2% OPCAB versus 10% ONCAB; P=0.05). Notably, in CORONARY, no differences in repeat revascularization by PCI or CABG were found at 5 years (2.8% versus 2.3% [P=0.29] and 0.4% versus 0.2% [P=0.17]).

IR in the OPCAB group has been correlated with long-term mortality. In a large study in which 5423 on-pump patients were propensity matched with 5423 OPCAB patients, the latter had higher prevalence of IR (6.9% ONCAB versus 13.6% OPCAB; P<0.001). Long-term mortality was significantly higher for patients undergoing incomplete OPCAB.[88]

In a recent analysis of >13 000 patients from a single institution, a detrimental effect of IR on survival was demonstrated when at least 1 territory was not revascularized in OPCAB patients. Interestingly, a similar effect was evident only when 2 coronary territories were left ungrafted in the on-pump series; this finding suggests that the pathogenesis and clinical consequences of IR may differ between the 2 techniques.[89]

It must be noted, however, that the interpretation of the literature on the subject is problematic for several reasons. The definition of IR varies markedly among studies, making comparisons between trials very difficult. In addition, IR can be a surrogate marker of a greater burden and complexity of coronary disease and a worse risk profile for the patient. In fact, variables such as reduced EF, advanced age, heart failure, and reoperation have been associated with both IR and survival.[90] In these situations, it is difficult to determine the effect of IR per se and the role of various preoperative risk factors that are prevalent in the same patients.

In summary, IR is probably an explanation for the worse long-term outcomes of OPCAB and seems to be related to surgeon's experience.

The Role of Surgeon Experience

The individual surgeon's expertise in OPCAB and hospital volume have long been considered important determinants of outcome.[91]

RCTs suggesting increased risk with OPCAB have been criticized by those who believe that surgeon experience plays a major role in determining outcomes. In the ROOBY trial, in which OPCAB was associated with increased 5-year mortality (15.2% in the OPCAB group versus 11.9% in the on-pump group; P=0.02), the 53 participating surgeons enrolled an average of only 8 patients per year during the study period and had a high conversion rate to on-pump surgery (12%) and IR (18%).[40] Moreover, in 60% of the cases, a resident was the primary surgeon. In the GOPCABE study,[41] in which surgeons were required to be established experts with an average of 514 OPCAB procedures (median: 322), no significant differences between OPCAB and on-pump surgery were found. In the CORONARY trial, each procedure was performed by a surgeon who had expertise in the specific type of surgery (>100 cases using the specific technique, off-pump or on-pump) and similar 5-year outcomes with OPCAB and ONCAB were reported.[27]

Among the observational studies, Lapar et al found a significant surgeon volume–outcome relationship for mortality after OPCAB with a threshold of >50 operations per year.[92] Glance and colleagues, however, in a registry study from the New York State Database including 36 930 patients and 181 surgeons at 33 hospitals, did not find any association between OPCAB surgeon case volumes and mortality.[91]

In a recent post hoc analysis of the ART trial including 1260 and 1700 OPCAB and on-pump patients, respectively,[93] OPCAB performed by "sporadic" OPCAB surgeons (1–5 OPCAB procedures) presented a higher rate of conversion (12.9%) and a higher rate of operative mortality (4.8%) compared with ONCAB despite similar distribution of risk factors. OPCAB performed by 3 high-volume OPCAB surgeons (>60) showed a very low conversion rate (1%) and 5-year mortality comparable to ONCAB performed by 95 "on-pump only" surgeons. According to the STS ACSD, 84% of participating centers performed <50 off-pump cases per year, 34% of surgeons performed no off-pump operations, and 86% of surgeons performed <20 off-pump cases per year.[94] A recent analysis of the US NIS[95] showed that OPCAB performed in low-volume centers and by low-volume surgeons was associated with significantly increased risk-adjusted mortality. In contrast, OPCAB was associated with lower risk adjusted mortality when performed in high-volume hospitals (≥164 cases/year) and by high-volume surgeons (≥48 cases/year).

To summarize, it seems likely that the unique technical challenges of OPCAB may lead to poorer outcomes during each surgeon's "learning curve." To minimize the learning curve effect, appropriate patient selection, individualized grafting strategy, peer-to-peer training of the entire team, and graded clinical experience are of paramount importance.

Intraoperative Conversion From Off-Pump to On-Pump

An intraoperative switch from an OPCAB to an ONCAB approach is described as *intraoperative conversion* (IOC).[96]

IOC has been classified as *elective*, in which the change from OPCAB to ONCAB is aimed at the prevention of hemodynamic instability and occurs before the start of any distal coronary anastomosis, and *emergent*, in which the conversion takes place following the onset of hemodynamic instability and typically after the start of the construction of a distal anastomosis.

The reported rate of IOC is quite broad. In a recent analysis of the STS ACSD involving over 196 000 patients, the reported conversion rate was 5.5% of which 50% were elective.[97]

In a meta-analysis including 18 870 patients, IOC occurred in 4.9% of the cases.[98] In the CORONARY trial, the rate of IOC was 7.9%,[99] ranging from 0% to 60% among hospitals. The highest rates of IOC were reported before cardiac manipulation (43.5%) and grafting of the LAD (18.3%), whereas IOC before grafting of the lateral and inferior walls was less frequent (9.7% and 3.8%, respectively). In 15.1% of the cases, hemodynamic instability occurring soon after the induction of anesthesia led surgeons to convert before starting surgery.

The most common reason for IOC is hypotension (32.3%), followed by either small size (26.9%) or intramuscular course of target vessels (22.6%), ischemia (17.7%), and arrhythmias (11.3%); less common reasons were hemorrhage, graft occlusion, calcified aorta, and need for concomitant surgery.[96,99]

Elective IOC is usually well tolerated and associated with no increase in operative mortality.[96,99,100]

In contrast, emergency IOC is associated with significantly increased mortality risk.[96] In an analysis based on the STS ACSD, Keeling et al[97] reported observed to expected mortality of 1.4 for an elective IOC, 1.6 for emergency IOC for visualization reasons, and 2.7 for emergency IOC for hemodynamic instability. In the previously cited meta-analysis, emergency conversion raised the OR of mortality to 6.99 (95% CI, 5.18–9.45).[98] In addition to the noted increased mortality, IOC is also associated with increased risk of almost all perioperative complications including myocardial ischemic injury, stroke, renal failure, and prolonged ventilation.[97,100,101] Furthermore, IOC is associated with increased costs[102] as well as hospital readmissions and infectious complications.[103] Midterm and event-free survival is significantly reduced for patients who undergo IOC.[64,104]

Identifying patients at high-risk for IOC a priori and avoiding an ill-fated attempt at OPCAB likely constitutes the best strategy to improve OPCAB outcomes. Keeling et al[97] showed that older age, EF <35%, preoperative need for intra-aortic balloon pump, increasing number of diseased native coronary vessels, history of congestive heart failure, and urgent status of surgery are all independent predictors of IOC. Other identified risk factors for IOC are left main coronary artery disease, intramyocardial course of coronary targets, reoperative procedures, and increasing number of coronary grafts constructed.[99,100,105]

The rate of IOC declines with increasing OPCAB surgeon and institutional experience.[100,101]

In summary, IOC occurs in a relatively small percentage of OPCAB cases, although the incidence is related to surgeon experience. Elective IOC is usually a benign event, whereas emergency IOC is associated with significantly worse outcomes.

Comparison of Hospital Costs Between Off- and On-Pump CABG

Controlling costs in health care continues to be a challenge, and CABG, as one of the most frequently performed procedures in the world, remains a visible priority. Indeed, OPCAB was initially embraced as a promising procedure to reduce costs associated with CABG.[106]

Despite extensive research and multiple published studies during the past 2 decades, there continues to be debate regarding cost advantages of one versus the other approach.

Table 2 summarize the most important series comparing the cost of off- and on-pump CABG.

Scott et al,[116] in an observational study, found that patients undergoing ONCAB had significantly longer time to extubation, increased blood use, longer intensive care unit and postoperative lengths of stay, and higher in-hospital mortality than patients undergoing OPCAB, which would translate into significantly higher expenses associated with ONCAB. Similarly, in a large propensity-matched registry,[112] total costs were higher for ONCAB. Specifically, the operative procedure showed similar costs (roughly $5000), but other in-hospital costs including surgical devices, intensive care unit, cardiac ward, and blood products were significantly higher in patients undergoing ONCAB. At 1-year follow-up, this difference persisted ($12 000 for OPCAB versus $14 000 for ONCAB; $P<0.001$).

In contrast, data from the CORONARY trial showed no difference in costs between the 2 techniques.[115] During the index hospitalization, the cost for patients undergoing OPCAB was $8626 compared with $8567 for ONCAB, with a nonsignificant difference of $59. At follow-up, this trend of neutrality continued ($37 more for OPCAB at 6 months and $28 less for OPCAB at 1 year). A sensitivity analysis was also performed to evaluate the potential influence of supplies for the 2 surgical strategies. When OPCAB supplies cost $1000 less than ONCAB supplies, the cost savings with OPCAB were roughly $1000. However, increasing the cost of off-pump supplies to $2000 showed a linear increase in the incremental cost up to cost saving of $1000 for on-pump surgery. Alternatively, the ROOBY trial[117] reported significant cost saving with ONCAB ($56 023 versus $59 623; $P=0.05$). This finding was also confirmed by a large retrospective study (63 000 patients)[113] in which multivariable regression analysis showed a higher final cost by $1497 per patient in those

Table 2. Overview of the Series Comparing the Cost of OPCAB and ONCAB

First Author	Year	Study Design	Number of Patients; Cost Benefit	
			Off-Pump	On-Pump
Arom[107]	1999	Retrospective, hospital costs	62; 21% decreased costs	243
Boyd[108]	1999	Retrospective, hospital costs	30; 14% decreased costs	60
Ascione[109]	1999	Prospective, randomized hospital costs	100; 30% decreased costs	100
Nathoe[110](OCTOPUS trial)	2003	Multicenter, prospective, randomizedhospital and 1-year costs	142; hospital: 14% decreased costs, $P<0.01$;1 year: 12% decreased cumulative costs ($P<0.01$)	139
Puskas[111]	2004	Prospective, randomizedhospital and 1-year costs	100; hospital: 11% decreased costs ($P=0.002$)1 year: 8% decreased cumulative costs ($P=0.08$)	100
Lamy[112]	2006	Propensity-matched registry	1233; 1-year total costs: 15% decreased ($P<0.001$)	1233
Chu[113]	2009	Data from Nationwide Inpatient Sample 2004	14 389; $1497 (95% CI, $779–$2216) more in overallhospitalization costs in OPCAB than ONCAB	48 658
Shroyer[38](ROOBY trial)	2009	Multicenter prospective, randomizedhospital costs	1104	1099 Hospital: 6% decreased costs ($P=0.05$)
Houlind[114](DOORS trial)	2013	Multicenter, prospective, randomizedhospital and reintervention costs	450; hospital and reinterventions: 7% decreased costs	450
Lamy[115](CORONARY trial)	2014	Multicenter, prospective, randomizedhospital and 1-year costs	2375	2377; hospital: 1% decreased costs (P=ns); 1 year: 1% decreased cumulative costs (P=ns)
Lamy[39](CORONARY trial)	2016	Multicenter, prospective, randomized5-year costs	2375	2377; 5 years: 1% decreased cumulative costs (P=ns)

CABG indicates coronary artery bypass grafting; CORONARY, CABG Off- or On-Pump Revascularization; DOORS, Danish On-pump Off-pump Randomization Study; OCTOPUS, A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients trial; ONCAB, on-pump coronary artery bypass surgery; OPCAB, off-pump coronary artery bypass surgery; ROOBY, Randomized On/Off Bypass.

treated by OPCAB ($P<0.001$). Factors influencing the final cost of off-pump surgery were age >65 years, number of grafts, duration of anesthesia, very low EF, and low to medium hospital OPCAB volume.[115,118] Interestingly, no difference in cost was found in the CORONARY trial[118] among the different geographic areas for ONCAB and OPCAB.[115]

It must be noted that the cost analyses should be extrapolated to individual programs with caution because of the high variability in the cost of devices for different institutions and countries.

To summarize, no clear evidence shows that OPCAB significantly reduces in-hospital costs.

Anaortic, Total Arterial, Off-Pump CABG

The original thesis of OPCAB was that removing the CPB from the procedure would reduce pump-related inflammation, end-organ injury, and stroke. The vast majority of these procedures were performed using an in situ LIMA to the LAD and ≥1 proximal aortocoronary vein grafts placed onto the ascending aorta using a partial-occlusion clamp.

Anaortic OPCAB refers to a distinct off-pump technique with complete avoidance of aortic manipulation. This may prevent dislodgement and embolization of atheromatous plaque in the aorta and reduce the risk of stroke.[119] In situ grafts are used including one or both of the internal mammary arteries (and the gastroepiploic, in some cases) to avoid the need for proximal aortocoronary anastomoses and the associated aortic manipulation. Composite grafts are constructed as required including “T” or “Y” grafts or tandem or “I” grafts if an internal mammary artery is extended with a second conduit. Consequently, this technique also has a high percentage of total arterial conduits.

No adequate RCT has compared anaortic OPCAB to ONCAB. However, in a recent network meta-analysis comparing ONCAB, OPCAB with a partial-occlusion clamp, anaortic OPCAB, and OPCAB with a Heartstring "clampless device," the anaortic technique was found to result in superior short-term outcomes. Anaortic OPCAB resulted in statistically significant reductions in postoperative stroke (−78% versus ONCAB, −66% versus OPCAB with a partial-occlusion clamp; −52% versus OPCAB with a Heartstring device) and early mortality (−50% versus ONCAB; −40% versus OPCAB with a Heartstring device, −20% versus OPCAB with a partial-occlusion clamp), as well as renal failure, bleeding complications, and atrial fibrillation, and shorter length of intensive care unit stay.[120]

The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial remains the most influential study comparing CABG and PCI. The often quoted stroke rate of 2.2% for CABG versus 0.6% for PCI is a significant factor driving patients towards PCI, despite the proven long-term survival benefit and freedom from reintervention with CABG.[121] The CABG group in this trial included both on- and off-pump patients, and the percentage of anaortic patients is not known. Indirect comparisons from the literature show that the anaortic technique compares favorably with PCI (0.4% risk of stroke in the aforementioned network meta-analysis)[120] and suggests that a formal comparative RCT would be justified.

Minimally Invasive CABG, Total Endoscopic Coronary Artery Bypass, and HCR

The sequelae associated with the median sternotomy can affect postoperative quality of life and recovery. It has been estimated that more than a quarter of patients still have chronic non-cardiac chest pain 1 year after sternotomy, and this does not specifically relate to the harvest of the internal thoracic artery.[122] The future of surgical coronary revascularization must therefore involve ways to perform effective surgical revascularization without sternotomy.

The development of minimally invasive coronary surgical techniques has been limited by the difficulty in accessing and performing anastomosis in multiple different areas of the heart through a single, small, nonsternotomy incision. Three main options for the performance of CABG without sternotomy are now available (Table 3): (1) minimally invasive CABG, in which all areas of the heart are bypassed via a small left anterolateral thoracotomy, usually without the use of the heart–lung machine[123]; (2) robotic total endoscopic coronary bypass grafting, in which robotic techniques are used not only for internal mammary artery harvest but also for the performance of all graft anastomoses[124]; and (3) HCR, which combines the performance of a single LIMA-LAD graft via a small anterolateral thoracotomy, with PCI to the other myocardial territories of the heart that require revascularization.[125]

Table 3. Comparison of Nonsternotomy OPCAB Modalities

	MICS CABG	TECAB	HCR
Safety and efficacy	+++	+++	+++
Avoidance of CPB	++	+	+++
Avoidance of invasiveness	++	++	+++
Availability outside of expert centers	+	···	++
Completeness of surgical revascularization	+++	++	+
Ability to perform multiarterial grafting	++	+++	···
Cost containment vs CABG	+++	+	++

CABG indicates coronary artery bypass grafting; CPB, cardiopulmonary bypass; HCR, hybrid coronary revascularization; MICS CABG, minimally invasive coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass surgery; TECAB, total endoscopic coronary artery bypass grafting.

So far, observational data have suggested that these procedures are safe and that patients recover significantly faster than with CABG in the early postoperative period.[125–127] Furthermore, there may also be benefits related to periprocedural morbidity compared with CABG.[125]

No RCT to date has compared minimally invasive techniques with traditional CABG. Two trials are currently under way to evaluate minimally invasive CABG and HCR: the MIST (Minimally Invasive Coronary Surgery Compared to Sternotomy Coronary Artery Bypass Grafting) trial and the National Heart, Lung, and Blood Institute–funded Hybrid Coronary Revascularization Trial. These prospective trials are being undertaken to ascertain, respectively, the amount of recovery benefit that minimally invasive CABG may have over sternotomy CABG and whether HCR is superior to a strategy of multivessel PCI regarding 5-year incidence of major adverse cardiac events. The results of these trials will shed light on the role of nonsternotomy CABG in clinical practice.

Conclusions

More than 30 years after the introduction of OPCAB, its role in coronary surgery remains debated. In the general population, OPCAB has been associated with similar short-term outcomes, at least when performed by experienced surgeons. In the long term, inferior outcomes have been reported with OPCAB. High-risk patients can potentially benefit from OPCAB, and this seems to be particularly relevant for patients at high risk of intraoperative stroke who are operated with the anaortic technique, but this hypothesis has not been adequately tested in randomized studies. The use of minimally invasive and hybrid approaches is promising.

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